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14. ABSTRACT
Breast cancer continues to be the most common and second deadliest cancer of women living in the United States.1, 2 It is thought that obesity and chronic inflammation play an important role in increasing risk of breast cancer in humans. 3-5 There is evidence suggesting change in dietary habits including drinking green tea may modify the risk of breast cancer development. This decrease in breast cancer risk may be mediated through the proposed effect of green tea intake on body weight and inflammation. 6, 7 The purpose of this training grant is to examine the effects of green tea extract supplementation for one year on obesity-related hormones and inflammatory biomarkers as two of the purported mechanisms by which green tea may result in reducing breast cancer risk. This research study is a randomized, placebo-controlled, double-blind in a subgroup of 300 healthy postmenopausal obese and overweight women with differing COMT genotypes of the parent grant called "Green Tea and Reduction of Breast Cancer Risk". A major up-to-date achievement of this study includes completing the study for 114 subjects. This accounts for 38% of the total sample size. Another achievement includes recruiting and randomizing 108 more subjects into the study. It is anticipated that the recruitment for this training grant will be finished by the end of July 2012. Finally, the analyses of all biological samples are scheduled to take place at the beginning of April 2012.

15. SUBJECT TERMS
Green tea, Breast cancer risk, Obesity, epigallocatechin-3-gallate (EGCG), appetitive hormones, inflammatory biomarkers, postmenopausal women.

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INTRODUCTION

There are currently several lines of evidence suggesting green tea catechin supplementation is inversely associated with obesity and inflammation.[6, 7] As a result of the decrease in obesity and inflammation, there is a decreased breast cancer risk. However, the physiological mechanisms by which green tea supplementation may help to reduce breast cancer are unclear. The goal of this training grant is to investigate how green tea extract intake may lead to change in the obesity-related hormones as well as inflammatory biomarkers of healthy postmenopausal women with differing COMT genotypes. Particularly, this research project will measure glucose, glycosylated hemoglobin (HbA1c), appetitive hormones such as leptin, insulin, adiponectin, ghrelin, and inflammatory markers including interleukin-1b (IL-1b), IL-6, IL-8, tumor necrosis factor alpha (TNF-a), and high-sensitivity C-Reactive Protein (hs-CRP).

BODY

The human clinical trial proportion of this training grant has proceeded successfully so far. As of March 9, 2012, 558 women have been randomized and enrolled in the parent grant where 261 subjects have been eligible to be considered for this training grant. Among the eligible subjects for this training project, 114 women have completed the study, 108 are in the study, and 38 subjects have withdrawn from the study. These figures imply the PI has been successful in fulfilling 38% of the total target sample size up until now. Given the current enrolment rate, it is expected that the PI will be able to finish the recruitment by the end of July 2012, and consequently, to complete the study for the last subject by July 2013. However, it should be noted these projections do not meet recruitment of equal numbers of low and high activity COMT genotypes in each experiment group for this training grant. This is due to a potential problem raised with the slow recruitment of participants in the high activity COMT group. Since the high COMT genotype prevalence in the parent study population has been lower than expected, there is a small chance that the PI will not be able to enroll equal numbers of low and high activity COMT subjects in to the study. Given this genetic approach is part of the secondary hypothesis, and considering subjects are randomly allocated to the experiment groups, it is very unlikely that the study primary outcomes will be influenced.

Currently, the dropout rate for the parent grant and this training study are 13.2% and 14.6%, respectively. In terms of monitoring compliance, participants have been fairly compliant (above 90%) with the study protocol instructions for taking the study supplement pills. In addition, the PI has assisted in organizing, processing and aliquoting blood samples for the subjects who have either completed or started the study. Finally, he has also helped to administer the study questionnaires and has kept close contact with study participants through monthly phone calls or frequent emails.

As described in the Statement of Work document, analyses of all biological samples will not start until the second year of this grant proposal. The PI plans to start conducting the plasma sample analyses in early April 2012 with the aid of a trained lab technician.

As part of the training plan, the PI has also attended the weekly seminars offered by the University of Minnesota Masonic Cancer Center as well as the seminars presented in the PI's Food Science and Nutrition department. In addition, he attended the 5th International Workshop of Breast Densitometry and Breast Cancer Risk Assessment in San Francisco on June 9 and 10, 2011. Lastly, The PI will be attending the Obesity 2012 conference, the 30th Annual Scientific Meeting in San Antonio, Texas in September 2012.

Regarding academic training, the PI has made a significant progress towards completion of his doctorate degree in Human Nutrition at the University of Minnesota. A seminar presentation was given in the Food Science and Nutrition department of University of Minnesota in 2011, and a Master plan B degree was awarded while the PI was completing his PhD requirements in 2011. Also, the preliminary oral exam was successfully passed in August 2011. Finally, all required core and supporting courses as well as teaching requirements will be completed by the end of this current Spring 2012 semester (current cumulative GPA 3.69).

KEY RESERCH ACCOMPLISHMENTS

- Study completion for 114 women representing 38.0% of total target sample size
- Recruitment and randomization of 108 new participants
- Passing preliminary written and oral examinations, leading to doctoral candidate status
- Completing the remainder of required core coursework by the end of this current semester (Spring 2012)
- Contributing to recruitment of 558 subjects, and completing the study for 252 subjects of the parent grant (as of March 9, 2012)

REPORTABLE OUTCOMES

Since the clinical trial design of this training project is randomized, placebo-controlled, and double-blind, the PI cannot break the codes for treatment and control groups until the last subject completes the study. This means the PI can only start writing the manuscripts based on study outcomes when the last participant is done with the study, which will be sometime after August 2013. Meanwhile, the PI has helped to prepare an abstract for a poster presentation at the Obesity 2012, 30th Annual Scientific Meeting in Texas in September 2012. Please refer to the appendix for the copy of the submitted abstract. Also, the PI plans to work on publishing one or two manuscripts including

baseline data from the either parent study or the grant training project during the upcoming year.

The PI's academic tuition at the University of Minnesota, health benefits, a stipend for living expenses, and travel costs for attendance to the 2011 Breast Cancer Workshop in San Francisco have been covered from funds from this training grant.

CONCLUSION

This study is proceeding as proposed in the "Statement of Work". The study will continue to recruit for the next couple of months, and it will be completed for the last subject by July 2013. This training grant aims to assess the effects of green tea consumption for one year on obesity and energy balance-related biomarkers linked to breast cancer risk. To date, this will be the largest and the first long-term human study measuring changes in the obesity-related hormones as well as inflammatory biomarkers in postmenopausal women after receiving green tea extract supplementation. The results from this trial will allow us to understand the relationships among green tea supplementation, obesity, inflammation, and breast cancer risk.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics 2010. *CA cancer clin*. 2010; 60:277–300.

2. http://www.cancer.gov/cancertopics/types/breast

3. Eliassen AH, Colditz, GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA. 2006;* 296:193-201.

4. Ahn J, *et al.* Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med. 2007;* 167: 2091-2102.

5. Morris PG, *et al.* Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. *Cancer Prev Res (Phila).* 2011; 4:1021-9.

6. Cao H, *et al.* Green tea increases anti-inflammatory tristetraprolin and decreases pro-inflammatory tumor necrosis factor mRNA levels in rats. *Journal of Inflamm*. 2007; 4:1.

7. Nagao T, Hase T, Tokimitsu I. A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. *Obesity.* 2007;15:1473-1483.

APPENDIX 1

Poster abstract for Obesity 2012, 30th Annual Scientific Meeting, September 20-24, 2012 in San Antonio, TX

Long-term green tea extract consumption may reduce body weight in healthy postmenopausal women independent of other diet/lifestyle interventions.

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Green tea consumption has been associated with a reduction in adiposity, an independent risk factor for postmenopausal breast cancer. This pilot study assessed the effects of green tea extract (GTE) on body mass index (BMI) in postmenopausal women at high risk for breast cancer, and determined if these effects varied by genotype of catechol-O-methyl transferase (COMT), the primary enzyme responsible for metabolizing green tea catechins. A biostatistician not involved with the study conducted an interim analysis on 205 women who have completed the randomized double blind, placebo-controlled, parallel arm study (final n=800). Women consumed either GTE containing 800 mg epigallocatechin gallate (EGCG) or placebo capsules daily for 12 months and were instructed to maintain usual dietary/lifestyle behaviors. BMI was assessed at baseline and 12 months. At baseline, the women were an average 58.4±5.4 years old with an average BMI of 25.4±5.5 kg/m^2. In the entire group, there was no significant effect on BMI between GTE (n=100) and placebo (n=105). When the groups were stratified by COMT genotype, however, women in the A/A group (low activity) who consumed the GTE (n=27) showed a trend toward decreased BMI when compared with the placebo group (n=28) (-0.36±0.82 kg/m^2 vs +0.05±0.80 kg/m^2, *P*=0.06). No differences were evident between GTE and placebo groups for the A/G genotype (intermediate activity), and changes were reversed for the G/G genotype (high activity, +0.28± 1.62 kg/m^2 vs. -0.49± 0.93 kg/m^2 for the GTE and placebo, respectively; *P*=0.09). These data suggest that long-term exposure to GTE containing 800 mg EGCG may improve BMI, independent of other dietary/lifestyle interventions, in healthy postmenopausal women with the low-activity COMT genotype.